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10/686,092	10/14/2003	Karen W. Shannon	10030468-1	6820

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EXAMINER	
WHALEY, PABLO S	

ART UNIT	PAPER NUMBER
1631	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/686,092	SHANNON, KAREN W.	
	Examiner	Art Unit	
	PABLO WHALEY	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 December 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,6-16 and 26-30* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4, 6-16 and 26-30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Claims

Claims 1-4, 6-16 and 26-30 are pending.

Claims 1-4, 6-16 and 26-30 are rejected.

Claims 17-25 have been cancelled.

Withdrawn Rejections

The rejection of claims 1-4, 6-16 and 26-30 are rejected under 35 U.S.C. 112, second paragraph, is withdrawn in view of applicant's arguments, filed 12/17/2008.

The rejection of claims 1, 2, 3, 6, 7, 8, 9, 14-16, 26, 27, 28, 29, and 30 under 35 U.S.C. 103(a) as being made obvious by Collins in view of Lockhart is withdrawn in view of applicant's arguments that the instant application and Collins were co-owned by Agilent Technologies, filed 12/17/2008.

The rejection of claims 1, 2, 6-10, 12-16, and 26-30 under 35 U.S.C. 103(a) as being made obvious by Li in view of Relogio and Ben-dor is withdrawn in view of applicant's amendments, filed 12/17/2008.

The rejection of claims 1, 10, and 11 are rejected under 35 U.S.C. 103(a) as being made obvious by Li in view of Relogio and Ben-dor and further in view of Cao is withdrawn in view of applicant's amendments, filed 12/17/2008.

The rejection of claims 1-4, 7-9, 13-16, and 26-30 are rejected under 35 U.S.C. 103(a) as being made obvious by Sung in view of Relogio and Ben-dor is withdrawn in view of applicant's amendments, filed 12/17/2008.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 2, 6-10, 12-16, and 26-30 are rejected under 35 U.S.C. 103(a) as being made obvious by Li et al. (Bioinformatics, 2001, Vol. 17, No. 11, p.1067-1076), in view of Schena (BioEssays, 1996, Vol. 18, No. 5, p.427-431), in view of Relogio et al. (Nucleic Acids Research, 2002, Vol. 30, No. 11, p.1-10) and Ben-dor et al. (Journal of Computational Biology, 1999, Vol. 6, No. ¾, p. 281-297).

The following new grounds of rejections are necessitated by applicant's amendment filed 12/17/2008, which requires differential gene expression assays.

Li et al. teach a computer-implemented method and program called "ProbeSelect" for selecting an optimal number of DNA oligos for gene expression arrays. Identification and selection of candidate probes is based on selection criteria [Abstract, Fig. 2, and Table 1], frequency matching [p.1070, Col. 2, ¶ 2], free energy calculation [p.1071, Col. 1, ¶ 3], and sequence matching (and mismatching) [p.1071, Col. 1, ¶ 2], which are teachings for selection based on base composition and lack of homology. It is noted that

selection of mismatch sequences is interpreted as a teaching for 'lack of homology. Selection criteria directed to frequency calculation [p.1071, Col. 1, ¶1] and free energy calculation [p.1072, Col. 1, ¶1] and [Table 4], are teachings for empirical evaluation. Candidate probes are evaluated using three different model organisms (i.e. experimental conditions), including *E. coli* bacterial cell lines [p.1074, Col. 1, ¶1]. The "ProbeSelect" computer program as described equates to a computational analysis system [p.1069, Col. 2, ¶3]. Optimal probes are output to a user [Table 1 and 2]. Li et al. also teach subjecting arrays to experimental conditions for producing gene expression data [p.1067, Col. 2, DNA chips].

Li et al. does not specifically teach a step for empirically evaluating candidate probes under differential gene expression assay experiments that employ a different nucleic acid sample pair, and wherein said target nucleic acid is differentially expressed in at least one sample pair, as in claims 1 and 26, step b.

Li et al. does not specifically teach limitations directed to clustering data based on gene expression, as in claims 1 and 26 (step c), and claims 13 and 26.

Li et al. does not teach deriving a similarity matrix based on expression vectors, wherein probes have similar expression patterns, as in claims 7, 8, 28, and 29.

Li et al. does not specifically teach identifying sequences suitable for use as a substrate probes by evaluating probe sequences not among groups of candidate probe sequences that satisfy a signal intensity threshold and exhibit substantially no change in signal across different gene expression assays, as in claims 1 and 26 (step d).

Schena teaches empirically evaluating probes using differential gene expression assays [Abstract]. In particular, Schena teaches two-color quantitative monitoring scheme for differential gene expression monitoring using microarrays containing a plurality of different samples, different genes, and different probes [p.428, Fig. 2, Table 1, p.429, Col. 1, and Fig. 3]. The motivation for using microarrays

in monitoring differential gene expression would have been to provide a rapid method for identifying changes in expression that accompany drug treatments [p.430, Col. 2, last ¶].

Ben-dor teaches clustering of gene expression data obtained from the hybridization of target sequences to a microarray [Abstract, p.281-282], which shows clustering of candidate probe sequences based on empirical gene expression data. Ben-dor teaches measured expression levels of genes in variable experimental conditions [p.282, ¶3], and clustered groups exhibiting substantially the same performance across a plurality of experimental conditions [p.291, Fig. A, Fig. B, and p.293, Color Plate 2 (A), Color Plate 3], as in claims 1 and 26 (step c). Ben-dor teaches obtaining gene expression data and representing data by a real-valued expression matrix (i.e. expression vector), deriving a similarity matrix, clustering genes based on the similarity data or on the expression data [p.282, ¶3], and displaying results [p.291, Fig. A-C], as in claims 1 (step c), 7, 26 (step c, e, and f), and 28. The clustering method of Ben-dor aims to identify sets of genes that behave similarly across different experimental conditions [p.282, ¶1], compares expression patterns for clustered based on intensity levels [Color Plate 2, Chart A], and performs clustering using an minimum intensity threshold [p.294, Section 4.3, Fig. 7, Fig. 8], wherein at least two sets exhibits similar performance. Ben-dor teaches a clustering routine using affinity thresholds to analyze assigned and probes not among the clusters [Fig. 2 and p.285, ¶1], as in claim 1, step d, wherein analysis stops when all data is clustered which shows affinity thresholds and no further evaluation if no non-clustered probes are present, as in claims 9 and 13.

Relogio teaches a method for identifying suitable sequences of oligonucleotide probes for use as microarray probes [Abstract, p.1, Col. 2, last ¶]. In particular, Relogio teaches a probe selection algorithm where probe are excluded based on specific conditions [p.2, Col. 1, ¶2]. Relogio teaches evaluating oligonucleotide probes under different experimental conditions, and identifying optimal probes based on probe sensitivity, specificity, and dynamic range [Abstract, Fig. 1 and 2, Table 1 and 2]. Relogio also shows their methods assist in the design of DNA microarrays used for sequence analysis [Introduction,

Col. 1, p.8, Discussion]. Relogio does not specifically teach evaluating any remaining probe candidates not among groups of candidate probes that satisfy a signal intensity threshold and exhibit no variation in signal, as in claims 1 and 26 (step d). However, this limitation would have been obvious to one of ordinary skill in the art since Relogio compares signal intensities for a plurality of groups of sequences with controls [Fig. 1B], identifies groups of probes with signal intensity values above and below a median value (i.e. threshold) [Table 2], and shows at least one pair of probes with substantially no variation in probe intensity across experimental groups [Table 1, 2, 3, 4, 9]. The motivation would have been to optimize the selection of oligonucleotide probes in order to improve microarray performance, as suggested by Relogio [p.1, Col. 2, last ¶].

It would have been obvious to someone of ordinary skill in the art at the time of the instant invention to modify the probe selection method of Li by empirically evaluating probes using differential gene expression assays, as in claims 1 and 26, step b, since Schena teaches differential gene expression monitoring using microarrays containing a plurality of different samples, different genes, and different probes [p.428, Fig. 2, Table 1, p.429, Col. 1, and Fig. 3]. The motivation for using differential gene expression monitoring using microarrays would have been to provide a rapid method for identifying changes in expression that accompany drug treatments, as suggested by Schena [p.430, Col. 2, last ¶] and Sung [p. 2, Col. 1, ¶3].

It would have been obvious to someone of ordinary skill in the art at the time of the instant invention to modify the probe selection method of Li by empirically evaluating candidate probes, as in claims 1 and 26, step b, since Ben-dor teaches measured expression levels of genes in variable experimental conditions [p.282, ¶3]. The motivation would have been to simultaneously analyze thousands of genes across different conditions by clustering gene expression patterns, as suggested by Ben-dor [Abstract].

It would have been obvious to someone of ordinary skill in the art at the time of the instant invention to modify the probe selection method of Li by clustering data based on gene expression, as in claims 1 and 26 (step c), and claims 13 and 26, since Ben-dor shows applications of their method specifically with microarray gene expression data [p.292, Section 4.2]. The motivation would have been to rapidly analyze gene expression data produced by candidate probes and ensure selection of optimal probes [Li et al., p.1076, Col. 1, ¶1].

It would have been obvious to someone of ordinary skill in the art at the time of the instant invention to modify the probe selection method of Li by deriving a similarity matrix based on expression vectors, wherein probes have similar expression patterns, as in claims 7, 8, 28, and 29, since Ben-dor shows gene expression data, expression vectors, and deriving a similarity matrix [p.282, ¶3], p.291, Fig. A-C]. The motivation would have been to identify sets of genes that behave similarly across different experimental conditions, as suggested by Ben-dor [p.282, ¶1].

It would have been obvious to someone of ordinary skill in the art at the time of the instant invention to modify the probe selection method of Li by identifying sequences suitable for use as a substrate probes by evaluating probe sequences not among groups of candidate probe sequences that satisfy a signal intensity threshold and exhibit substantially no change in signal across different gene expression assays, as in claims 1 and 26 (step d), since Ben-dor teaches an algorithm that allows for the analysis of probe data that has not been assigned to any cluster [Fig. 2], since Ben-dor identifies probes with substantially the same performance across different experiments using an minimum intensity threshold [Color Plate 2, Chart A], p.294, Section 4.3, Fig. 7, Fig. 8], and since Relogio identifies suitable sequences based on signal intensity thresholds [Fig. 2, Table 7] and shows at least one pair of probes with substantially no variation in probe intensity across experimental groups [Table 1, 2, 3, 4, 9]. The motivation would have been to rapidly analyze gene expression data produced by candidate probes or

to provide additional information for ensuring selection of optimal probes [Li et al., p.1076, Col. 1, ¶1], and to identify optimal probes for use in microarrays [Relogio, Introduction, Col. 1, p.8, Discussion].

Claims 1, 10, and 11 are rejected under 35 U.S.C. 103(a) as being made obvious by Li et al. (Bioinformatics, 2001, Vol. 17, No. 11, p.1067-1076), in view of Schena (BioEssays, 1996, Vol. 18, No. 5, p.427-431), in view of Relogio et al. (Nucleic Acids Research, 2002, Vol. 30, No. 11, p.1-10), and in view of Ben-dor et al. (Journal of Computational Biology, 1999, Vol. 6, No. ¾, p. 281-297), as applied to claims 1, 2, 6-10, 12-16, and 26-30, above, and further in view of Cao et al. (Cross Comparison of DNA Microarray Platforms, Alliance for Cellular Signaling Laboratories, Sept. 26, 2003, p.1-23).

Li et al., Schena, Relogio, and Ben-dor et al. make obvious a method for selecting an optimal number of probes for use in gene expression arrays, as set forth above and applied to claims 1, 2, 6-10, 12-16, and 26-30.

Li et al., Schena, Relogio, and Ben-dor et al. do not specifically teach log-ratio limitation as in claims 10 and 11. However, Ben-dor et al. clearly teach and suggest the calculation of log-ratios of intensities [p.292, ¶ 1].

Cao et al. teach a method for comparing the reproducibility and sensitivity of several microarray platforms, including the Affymetrix GeneChip, custom cDNA arrays, and custom oligo arrays [Abstract]. More specifically, Cao et al. teach calculation of "log-ratio" values across a number of different experimental conditions [p.8] and values in the range of –0.16 to 0.44 [p.10], as in claims 10 and 11.

It would have been obvious to someone of ordinary skill in the art at the time of the instant invention to modify the probe selection method made obvious by Li, Schena, Relogio, and Ben-dor using log-ratio calculations taught by Cao et al., since Ben-dor et al. suggests the assessment of probes by taking the log-ratio of probe intensities [p.292, ¶ 1]. One of ordinary skill in the art would have been

motivated to combine the above teachings in order to compare gene expression data for optimal probes that are selected using different platforms [Cao et al., p.6], resulting in the practice of the instant claimed invention.

Claims 1-4, 7-9, 13-16, and 26-30 are rejected under 35 U.S.C. 103(a) as being made obvious by Sung et al. (Proceedings of the Computational Systems Bioinformatics (CSB'03), 11-14 August 2003, p.1-10), in view of Schena (BioEssays, 1996, Vol. 18, No. 5, p.427-431), in view of Relogio et al. (Nucleic Acids Research, 2002, Vol. 30, No. 11, p.1-10) and Ben-dor et al. (Journal of Computational Biology, 1999, Vol. 6, No. ¾, p. 281-297).

Sung et al. teach a computer-implemented method for designing probes for microarrays [Abstract]. Sung shows identifying probes using a program (i.e. FindProbe), wherein three types of selection criteria are used [Section 2.1 and 2.2] including homogeneity (i.e. base content), proximity to 3' end of probes [Section 4: Sensitivity filtering], and matching and mismatching of sequences (i.e. lack of homology) [Section 5.2], as in claims 1, 2, 3, and 27. It is noted that sensitivity filtering reduced probes that form secondary structures (i.e. overlap) [Section 4], and therefore has been broadly interpreted as a teaching for minimization of candidate probes that overlap with each other, as in claim 4. Sung also shows evaluating their method of probe selection based on experimental results [Section 1.2, ¶4] and experimentally evaluating candidate probes in different experimental conditions [p.7, Section 6, Col. 1, and Table 2 and 5] as in claims 1 and 26 (step b). The "FindProbe" program is a teaching for a computational system, as in claims 14-16 and 30.

Sung et al. does not specifically teach a step for empirically evaluating candidate probes under differential gene expression assay experiments that employ a different nucleic acid sample pair, and wherein said target nucleic acid is differentially expressed in at least one sample pair, as in claims 1 and 26, step b.

Sung et al. does not specifically teach limitations directed to clustering data based on gene expression, as in claims 1 (step c), claim 26 (step c, e, and f), and claims 13 and 26.

Sung et al. does not teach deriving a similarity matrix based on expression vectors, wherein probes have similar expression patterns, as in claims 7, 8, 28, and 29.

Sung et al. does not specifically teach identifying sequences suitable for use as a substrate probes by evaluating probe sequences not among groups of candidate probe sequences that satisfy a signal intensity threshold, as in claims 1 and 26 (step d).

Schena teaches empirically evaluating probes using differential gene expression assays [Abstract]. In particular, Schena teaches two-color quantitative monitoring scheme for differential gene expression monitoring using microarrays containing a plurality of different samples, different genes, and different probes [p.428, Fig. 2, Table 1, p.429, Col. 1, and Fig. 3]. The motivation for using microarrays in monitoring differential gene expression would have been to provide a rapid method for identifying changes in expression that accompany drug treatments [p.430, Col. 2, last ¶].

Ben-dor teaches clustering of gene expression data obtained from the hybridization of target sequences to a microarray [Abstract, p.281-282], which shows clustering of candidate probe sequences based on empirical gene expression data. Ben-dor teaches measured expression levels of genes in variable experimental conditions [p.282, ¶3], and clustered groups exhibiting substantially the same performance across a plurality of experimental conditions [p.291, Fig. A, Fig. B, and p.293, Color Plate 2 (A), Color Plate 3], as in claims 1 and 26 (step c). Ben-dor teaches obtaining gene expression data and representing data by a real-valued expression matrix (i.e. expression vector), deriving a similarity matrix, clustering genes based on the similarity data or on the expression data [p.282, ¶3], and displaying results [p.291, Fig. A-C], as in claims 1 (step c), 7, 26 (step c, e, and f), and 28. The clustering method of Ben-dor aims to identify sets of genes that behave similarly across different experimental conditions [p.282, ¶1], compares expression patterns for clustered based on intensity levels [Color Plate 2, Chart A], and performs

clustering using an minimum intensity threshold [p.294, Section 4.3, Fig. 7, Fig. 8], wherein at least two sets exhibits similar performance. Ben-dor teaches a clustering routine using affinity thresholds to analyze assigned and probes not among the clusters [Fig. 2 and p.285, ¶1], as in claim 1, step d, wherein analysis stops when all data is clustered which shows affinity thresholds and no further evaluation if no non-clustered probes are present, as in claims 9 and 13.

Relogio teaches a method for identifying suitable sequences of oligonucleotide probes for use as microarray probes [Abstract, p.1, Col. 2, last ¶]. In particular, Relogio teaches a probe selection algorithm where probe are excluded based on specific conditions [p.2, Col. 1, ¶2]. Relogio teaches evaluating oligonucleotide probes under different experimental conditions, and identifying optimal probes based on probe sensitivity, specificity, and dynamic range [Abstract, Fig. 1 and 2, Table 1 and 2]. Relogio also shows their methods assist in the design of DNA microarrays used for sequence analysis [Introduction, Col. 1, p.8, Discussion]. Relogio does not specifically teach evaluating any remaining probe candidates not among groups of candidate probes that satisfy a signal intensity threshold and exhibit no variation in signal, as in claims 1 and 26 (step d). However, this limitation would have been obvious to one of ordinary skill in the art since Relogio compares signal intensities for a plurality of groups of sequences with controls [Fig. 1B], identifies groups of probes with signal intensity values above and below a median value (i.e. threshold) [Table 2], and shows at least one pair of probes with substantially no variation in probe intensity across experimental groups [Table 1, 2, 3, 4, 9]. The motivation would have been to optimize the selection of oligonucleotide probes in order to improve microarray performance, as suggested by Relogio [p.1, Col. 2, last ¶].

It would have been obvious to someone of ordinary skill in the art at the time of the instant invention to modify the probe selection method of Sung by empirically evaluating candidate probes, as in claims 1 and 26, step b, since Ben-dor teaches measured expression levels of genes in variable experimental conditions [p.282, ¶3]. The motivation would have been to simultaneously analyze

thousands of genes across different conditions by clustering gene expression patterns, as suggested by Ben-dor [Abstract].

It would have been obvious to someone of ordinary skill in the art at the time of the instant invention to modify the probe selection method of Sung by empirically evaluating probes using differential gene expression assays, as in claims 1 and 26, step b, since Schena teaches differential gene expression monitoring using microarrays containing a plurality of different samples, different genes, and different probes [p.428, Fig. 2, Table 1, p.429, Col. 1, and Fig. 3]. The motivation for using differential gene expression monitoring using microarrays would have been to provide a rapid method for identifying changes in expression that accompany drug treatments, as suggested by Schena [p.430, Col. 2, last ¶] and Sung [p. 2, Col. 1, ¶3].

It would have been obvious to someone of ordinary skill in the art at the time of the instant invention to modify the probe selection method of Sung by clustering data based on gene expression, as in claims 1 (step c), claim 26 (step c, e, and f), and claims 13 and 26, since Ben-dor shows applications of their method specifically with microarray gene expression data [p.292, Section 4.2]. The motivation would have been to ensure that all candidate probes produce the expected expression patterns [Ben-dor et al., Abstract] or to determine which conditions that have the largest effect on clusters, as suggested by Ben-dor et al. [p.292 and 293, Section 4.2].

It would have been obvious to someone of ordinary skill in the art at the time of the instant invention to modify the probe selection method of Sung by using a similarity matrix based on expression vectors, wherein probes have similar expression patterns, as in claims 7, 8, 28, and 29, since Ben-dor shows gene expression data, expression vectors, and deriving a similarity matrix [p.282, ¶3], p.291, Fig. A-C]. The motivation would have been to identify sets of genes that behave similarly across different experimental conditions, as suggested by Ben-dor [p.282, ¶1].

It would have been obvious to someone of ordinary skill in the art at the time of the instant invention to modify the probe selection method of Sung by identifying sequences suitable for use as a substrate probes by evaluating probe sequences not among groups of candidate probe sequences that satisfy a signal intensity threshold, as in claims 1 and 26 (step d), since Ben-dor teaches an algorithm that allows for the analysis of probe data that has not been assigned to any cluster [Fig. 2], since Ben-dor identifies probes with substantially the same performance across different experiments using an minimum intensity threshold [Color Plate 2, Chart A], p.294, Section 4.3, Fig. 7, Fig. 8], and since Relogio identifies suitable sequences based on signal intensity thresholds [Fig. 2, Table 7] and shows at least one pair of probes with substantially no variation in probe intensity across experimental groups [Table 1, 2, 3, 4, 9]. The motivation would have been to rapidly analyze gene expression data produced by candidate probes or to provide additional information for ensuring selection of optimal probes [Li et al., p.1076, Col. 1, ¶1], and to identify optimal probes for use in microarrays [Relogio, Introduction, Col. 1, p.8, Discussion].

Response to Arguments

Applicant's arguments, filed 12/17/2008, that Li in view of Relogio and Ben-dor do not teach differential gene expression assays have been fully considered and are persuasive. Therefore this rejection is withdrawn. However, a new grounds of rejection has been applied in view of applicant's amendments, filed 12/17/2008. Applicant's arguments, filed 12/17/2008, that the teachings of Li in view of Relogio and Ben-dor have been fully considered but are not persuasive for the following reasons. In response to applicant's arguments that Li, Relogio, and Ben-dor do not teach clustering probes into groups that include candidate probe sequences that exhibit substantially the same performance across different gene expression assays and detect differential expression of target nucleic acid in at least one sample pair, Li shows performing different experiments using probe pairs that exhibit substantially the same performance [Tables 1, 2, 4]. The clustering method of Ben-dor aims to identify sets of genes that behave similarly

across different experimental conditions [p.282, ¶1], and shows clustering of probes using gene expression data and shows at least set of probes (i.e. sequence data) that exhibits substantially the same performance [Section 4.1 and Color Plate 1, Chart C]. In response to applicant's arguments that Li, Relogio, and Ben-dor do not teach identifying sequences of candidate probes by evaluating remaining probes not among groups that satisfy a signal intensity threshold and exhibit no variation in signal, as in claims 1 and 26 (step d), Ben-dor identifies probes with substantially the same performance using an minimum intensity threshold [Color Plate 2, Chart A], p.294, Section 4.3, Fig. 7, Fig. 8]. The algorithm also allows for the analysis of probe data that has not been assigned to any cluster [Fig. 2]. Relogio identifies suitable sequences through sensitivity and specificity optimization routines based on signal intensity thresholds [Fig. 2, Table 7], identifies groups of probes with signal intensity values above and below a median value (i.e. threshold) [Table 2], and shows at least one pair of probes with substantially no variation in probe intensity across experimental groups [Table 1, 2, 3, 4, 9]. Therefore, the examiner maintains that the combination of references teaches and/or makes obvious identifying sequences of candidate probes by evaluating remaining probes not among groups that satisfy a signal intensity threshold and exhibit no variation in signal.

Applicant's arguments, filed 12/17/2008, that Sung in view of Relogio and Ben-dor do not teach differential gene expression assays have been fully considered and are persuasive. Therefore this rejection is withdrawn. However, a new grounds of rejection has been applied in view of applicant's amendments, filed 12/17/2008. Applicant's arguments regarding the deficiencies of Sung in view of Relogio and Ben-dor are repeated from those set forth above and have been fully considered. In response, applicant's arguments are not persuasive for the reasons set forth above. In particular, regarding applicant's arguments that the combination of Sung in view of Relogio and Ben-dor do not teach identifying sequences of candidate probes by evaluating remaining probes not among groups that satisfy a signal intensity threshold and exhibit no variation in signal, as in claims 1 and 26 (step d), Ben-dor identifies

probes with substantially the same performance using an minimum intensity threshold [Color Plate 2, Chart A], p.294, Section 4.3, Fig. 7, Fig. 8]. The algorithm also allows for the analysis of probe data that has not been assigned to any cluster [Fig. 2]. Relogio identifies suitable sequences through sensitivity and specificity optimization routines based on signal intensity thresholds [Fig. 2, Table 7], identifies groups of probes with signal intensity values above and below a median value (i.e. threshold) [Table 2], and shows at least one pair of probes with substantially no variation in probe intensity across experimental groups [Table 1, 2, 3, 4, 9]. Therefore, the examiner maintains that the combination of references teaches and/or makes obvious identifying sequences of candidate probes by evaluating remaining probes not among groups that satisfy a signal intensity threshold and exhibit no variation in signal.

Applicant's arguments, filed 12/17/2008, that Li in view of Relogio, Ben-dor, and Cao do not teach differential gene expression assays have been fully considered and are persuasive. Therefore this rejection is withdrawn. However, a new grounds of rejection has been applied in view of applicant's amendments, filed 12/17/2008. Applicant's arguments regarding the deficiencies of Li in view of Relogio, Ben-dor, and Cao are repeated from those set forth above and have been fully considered. In response, applicant's arguments are not persuasive for the reasons set forth above. In particular, regarding applicant's arguments that the combination of Li in view of Relogio, Ben-dor, and Cao do not teach identifying sequences of candidate probes by evaluating remaining probes not among groups that satisfy a signal intensity threshold and exhibit no variation in signal, as in claims 1 and 26 (step d), Ben-dor identifies probes with substantially the same performance using an minimum intensity threshold [Color Plate 2, Chart A], p.294, Section 4.3, Fig. 7, Fig. 8]. The algorithm also allows for the analysis of probe data that has not been assigned to any cluster [Fig. 2]. Relogio identifies suitable sequences through sensitivity and specificity optimization routines based on signal intensity thresholds [Fig. 2, Table 7], identifies groups of probes with signal intensity values above and below a median value (i.e. threshold) [Table 2], and shows at least one pair of probes with substantially no variation in probe intensity across

experimental groups [Table 1, 2, 3, 4, 9]. Therefore, the examiner maintains that the combination of references teaches and/or makes obvious identifying sequences of candidate probes by evaluating remaining probes not among groups that satisfy a signal intensity threshold and exhibit no variation in signal.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Pablo Whaley whose telephone number is (571)272-4425. The examiner can normally be reached on 9:30am - 6pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Marjorie Moran can be reached at 571-272-0720. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Pablo S. Whaley/

Patent Examiner

Art Unit 1631

/John S. Brusca/
Primary Examiner, Art Unit 1631